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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/554,387	10/25/2005	Yoseph Shaaltiel	30570	1887

67801 7590 08/10/2011

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	PAPER NUMBER
1652	
MAIL DATE	DELIVERY MODE
08/10/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/554,387	SHAALTIEL ET AL.	
	Examiner	Art Unit	
	DELIA RAMIREZ	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *154 and 158-173* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *154 and 158-173* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 December 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :2/7/2011, 4/4/2011, 5/2/2011, 5/3/2011, 5/23/2011, 5/25/2011, 6/13/2011, 6/20/2011, 6/27/2011, 7/5/2011, 7/6/2011, 7/11/2011, 7/20/2011, 7/27/2011, and 8/2/2011.

DETAILED ACTION

Status of the Application

Claims 154, 158-173 are pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/28/2011 has been entered.

Applicant's amendment of claims 154, 158, 162, cancellation of claims 155-157, and addition of claims 168-173 as submitted in a communication filed on 4/28/2011 is acknowledged.

New claims 168-173 are directed to the subject matter previously examined. Claims 154 158-173 are at issue and are being examined herein.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

1. The information disclosure statements (IDS) submitted on 2/7/2011, 4/4/2011, 5/2/2011, 5/3/2011, 5/23/2011, 5/25/2011, 6/13/2011, 6/20/2011, 6/27/2011, 7/5/2011, 7/6/2011, 7/11/2011, 7/20/2011, 7/27/2011, and 8/2/2011 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Claim Objections

2. Claim 165 is objected to due to the recitation of "glucocerebrosidase protein of said plant cell". To clearly indicate that the protein is expressed in the plant cell, it is suggested the term be amended to recite "glucocerebrosidase protein expressed in said plant cell". Appropriate correction is required.

3. Claim 166 is objected to due to the recitation of "comprising plant cells of claim 161". It is suggested the term be amended to recite "comprising the plant cell of claim 161". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 158, 162, 164, 168, 170, 172 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by amendment.

6. Claim 158 (claims 162, 164 dependent thereon) is indefinite in the recitation of "protein of claim 154, having an increased affinity for, and uptake into macrophages, in comparison with the corresponding affinity and uptake of a recombinant human....produced in mammalian cells ...." for the following reasons. As written, the basis for comparison is variable because the claim does not require the comparison to be made with a protein having the same amino acid sequence as that of claim 154 produced in mammalian cells. The claim simply requires the comparison to be made with any recombinant human glucocerebrosidase protein made in mammalian cells. Since the basis for comparison is variable, making the determination as to whether prior art anticipates the claims is impossible. A reference can be at the same time anticipatory and non-anticipatory depending on what is used as the basis for comparison. For example, prior art may meet the limitations recited if the recombinant human glucocerebrosidase

comprises SEQ ID NO: X but may not meet the limitations recited if the recombinant human glucocerebrosidase comprises SEQ ID NO: Y. For examination purposes, it will be assumed that the claim reads "protein of claim 154, having an increased affinity for macrophages and increased uptake into macrophages, in comparison with the affinity for macrophages and uptake into macrophages of a recombinant human glucocerebrosidase consisting of SEQ ID NO: 8 produced in mammalian cells and having glucocerebrosidase activity". Correction is required.

7. Claim 168 (claims 170 and 172 dependent thereon) is indefinite in the recitation of "protein which comprises the amino acid sequence set forth in SEQ ID NO: 8....and is linked at its C terminus to a vacuolar targeting signal peptide as set forth in SEQ ID NO: 2, wherein said linkage is defined by the respective amino acid coordinates of SEQ ID NO: 14" for the following reasons. The phrase is completely unclear and confusing as one cannot determine how the linkage is related to SEQ ID NO: 14. Does the term imply that the protein comprises SEQ ID NO: 14? What is a coordinate of a sequence? For examination purposes no patentable weight will be given to the term "wherein said linkage is defined..... SEQ ID NO: 14". Correction is required.

Claim Rejections - 35 USC § 103

8. Claims 154, 158-167 remain rejected and new claims 168-173 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garger et al. (U.S. Publication 2002/0088024, published 7/4/2001; application No. 09/993059 filed on 11/13/2001), as evidenced by GenBank accession number P04062 GLCM_HUMAN GI:121283 (April 1, 1993) in view of Boller et al. (U.S. Patent No. 6054637, issued 4/25/2000). This rejection is applied to new claims 168-173 for the reasons of record and those set forth below.

9. It is noted that the instant rejection no longer relies on the teachings of Frijters et al. (NL-1012782, published 2/6/2001) in view of the fact that the claims as amended no longer require the ER

signal peptide taught by Frijters et al. (SEQ ID NO: 1). If the claims were to be amended in response to this Office action to require the ER signal peptide of Frijters et al., the teachings of Frijters et al. will be reintroduced.

10. Applicant argues that Boller et al. teach away from the vacuolar signal peptide of SEQ ID NO: 2 because this signal peptide lacks the first two amino acids disclosed by Boller et al. (SEQ ID NO: 29) and the prior art, as evidenced by Neuhaus et al. (PNAS 88:10362-10366 1991), Neuhaus et al., (The Plant Journal 5(1):45-54, 1994), and Neuhaus and Rogers (Plant Mol. Biol. 38:127-144 1998), teaches that deletions and substitutions within the native chitinase vacuolar signal peptide were detrimental to vacuolar targeting function. It is applicant's contention that due to the detrimental effects of deletions and substitutions within the native chitinase vacuolar signal peptide, the successful targeting of the polypeptide of SEQ ID NO: 8 to the vacuole with the signal peptide of SEQ ID NO: 2 was unexpected and unpredictable. With regard to Garger et al., applicant argues that Garger et al. teach exclusively secretion of the plant-expressed lysosomal enzymes into the interstitial fluid of whole plants and teach away from vacuolar targeting, citing paragraphs [0051], [106], [276] and [277] of Garger et al. Applicant argues that Garger et al. teach the existence of vacuolar sorting signals (CTPPs) in human lysosomal proteins and go to great lengths to eliminate the possibility of interference with secretion to the IF.

11. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection or avoid the rejection of new claims 168-173. New claims 168-173 are directed to a human glucocerebrosidase that comprises SEQ ID NO: 8 and is linked at the C-terminus to the polypeptide of SEQ ID NO: 2, compositions comprising said glucocerebrosidase, and a plant cell comprising said glucocerebrosidase. See Claim Rejections under 35 USC 112, second paragraph. The Examiner acknowledges the teachings of Boller et al., Neuhaus et al. Neuhaus and Rogers, and those of Garger et al. With regard to the argument that it is unpredictable as to whether the fragment of the signal peptide of SEQ ID NO: 29 of Boller et al. which is identical to the peptide of SEQ ID NO: 2 of the

instant application would act as a vacuolar signal peptide, it is noted that Boller et al. clearly teach fragments of the vacuolar signal peptide of SEQ ID NO: 29 (column 6, line 66-column 7 line 27) which are able to direct the desired protein to the plant vacuole, including the fragment of SEQ ID NO: 31 which is identical to the peptide of SEQ ID NO: 2 of the instant application except that it lacks the first amino acid (Asp) of SEQ ID NO: 2. Since the peptide of SEQ ID NO: 31 of Boller et al., which is a fragment of the signal peptide of SEQ ID NO: 29 that is smaller than the peptide of SEQ ID NO: 2 of the instant application, is able to target the desired protein to the plant vacuole, it follows that it is highly likely that the peptide of SEQ ID NO: 2 would also act as a vacuolar signal peptide because it contains all the elements of the peptide of SEQ ID NO: 31, which is described as being a vacuolar signal peptide.

With regard to the argument that Garger et al. teach that human lysosomal proteins comprise vacuolar signal peptides and that Garger et al. teach modification of the lysosomal protein to eliminate any possibility of interference with secretion to the IF, it is noted that the Garger et al. do not teach that human lysosomal proteins have vacuolar signal peptides. Instead, Garger et al. (paragraph [106]) teach that human Gal-A (alpha-galactosidase A) has a propeptide at the C-terminus (CTPP) which when expressed in plant cells appears to function for vacuolar localization, thus acting like a vacuolar signal peptide. Furthermore, it is noted that nowhere in the reference by Garger et al. there is a teaching or suggestion that all lysosomal proteins have such propeptide, or that human glucocerebrosidase has that propeptide. In addition, while it is agreed that Garger et al. modified the human Gal-A protein to delete this propeptide so that the human Gal-A was produced mostly in the IF, it is noted that there is no teaching in the reference of Garger et al. indicating that such propeptide was deleted in the human glucocerebrosidase or that the inactivation seen with Gal-A when present in plant vacuoles was also seen when producing human glucocerebrosidase. The teachings of Garger et al. pointed out by applicant (paragraphs [051], [106], [276], [277]), do not refer to the human glucocerebrosidase of the instant application but rather to Gal-A, a different enzyme. In view of the teachings of Boller et al. regarding the

advantages of directing proteins to the vacuole (i.e. vacuoles constitute the largest storage compartment in plants for dissolved substances), one of skill in the art would have been motivated to construct a fusion protein comprising the human glucocerebrosidase of SEQ ID NO: 8 linked at the C-terminus to a vacuole signal peptide such as that of SEQ ID NO: 2. There is a reasonable expectation of success at making the recited fusion protein because the molecular biology techniques to obtain such fusion are well known in the art. Also there is a reasonable expectation of success at directing the human glucocerebrosidase to the vacuole because the peptide of SEQ ID NO: 2 is a fragment of the signal peptide of SEQ ID NO: 29 that comprises all of the peptide of SEQ ID NO: 31, which is disclosed by Boller et al. as being a fragment of the signal peptide of SEQ ID NO: 29 also having vacuolar signal peptide activity. Therefore for the reasons of record and those set forth above, one would conclude that the claimed invention is obvious over the prior art of record.

12. Applicant has also submitted a declaration under 37 CFR 1.132 by inventor Yoseph Shaaltiel on 4/28/2011. In this declaration, Dr. Shaaltiel states that the claimed polypeptides have unexpected improved properties. According to Dr. Shaaltiel, the need for complex downstream processing to eliminate a signal peptide and the need to confirm removal of such signal peptide are of critical concern when producing human glycosylated proteins for therapeutic use, citing Cramer et al. (Current Topics in Microbiology and Immunology 240:95-108, 1992). Dr. Shaaltiel also refers to paragraphs [0106], [276]-[277] to support the argument that Garger et al. have cautioned against vacuolar targeting. Dr. Shaaltiel indicates that it was unexpected to find that by linking the peptide of SEQ ID NO: 2 to the C-terminus of the human glucocerebrosidase of SEQ ID NO: 8, one was able to obtain a fusion protein which (i) compares favorably with Cerezyme, considered the gold standard for recombinant glucocerebrosidase, and (ii) is safe as it has low rate of antibody formation, low incidence of hypersensitivity, and does not induce neutralizing antibodies. Dr. Shaaltiel also points out that the claimed fusion protein can be produced in plant cell culture economically and efficiently without the requirement of cleaving the

vacuolar signal peptide. The declaration further states that there is a long-felt need to produce human glucocerebrosidase by other methods beyond mammalian cell culture due to the cost and risks associated with mammalian cell culture, and that while others have attempted to produce human glucocerebrosidase in plants, production of a product which is catalytically active suitable for clinical trials have not been possible, citing U.S. Patent No. 5929304 by Radin et al. The declaration finally states that there is commercial success derived from the claimed invention (called taliglucerase alfa), citing different agreements between the assignee of the instant application and different companies and foreign governments.

13. The Examiner acknowledges the declaration by inventor Shaaltiel. Arguments regarding the teachings of Garger et al. cautioning against vacuolar targeting are not deemed persuasive because, as previously stated, the teachings of Garger et al. in paragraphs [0106], [276]-[277] do not refer to human glucocerebrosidase but rather Gal-A. See extensive discussion above regarding the teachings of Garger et al. It is reiterated herein that that there is no teaching or suggestion in the reference of Garger et al. indicating that there was a C-terminus propeptide deleted in the human glucocerebrosidase, or that the inactivation seen with Gal-A when present in plant vacuoles was also seen when producing human glucocerebrosidase.

With regard to arguments indicating the surprising properties of the fusion protein, it is noted that these properties are inherent to the product due to its structural characteristics. Therefore, the fusion protein of Garger et al. and Boller et al. would also have these properties by virtue of being a fusion protein that comprises the recited structural features and is produced in plant cells.

With regard to arguments indicating the failure to produce a product that can be used in clinical trials which is produced by plants, it is noted that the cited patent does not teach the failure to produce human glucocerebrosidase in plant vacuoles or the failure to produce any human glucocerebrosidase. Whether the fusion protein can be used in clinical trials or not is not relevant to the instant discussion

because the claims simply require a fusion protein comprising the peptide of SEQ ID NO: 2 linked to the C-terminus of the polypeptide of SEQ ID NO: 8, wherein said fusion polypeptide is glycosylated as recited. The fusion protein of Garger et al. and Boller et al. would have the recited glycosylation by virtue of its expression in plant cells.

With regard to arguments of commercial success, it is noted that the evidence provided refers to agreements to commercialize the fusion protein and not of actual sales of the fusion protein. Therefore, mere agreements to commercialize the claimed product are not deemed sufficient to show that the claimed product is a commercial success when no sales data is provided.

Double Patenting

14. Claims 154, 158-167 remain rejected and new claims 168-173 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 23-25 of copending Application No. 11/790991. This rejection as it relates to claims 168-173 is necessitated by amendment and is applied to new claims 168-173 for the reasons of record.

15. Applicant submits that issues of provisional and obviousness-type double-patenting will be further considered with respect to U.S. Application No. 11/790,991 upon indication by the examiner of allowable subject matter.

16. New claims 168-173 are directed to a human glucocerebrosidase that comprises SEQ ID NO: 8 and is linked at the C-terminus to the polypeptide of SEQ ID NO: 2, compositions comprising said glucocerebrosidase, and a plant cell comprising said glucocerebrosidase. See Claim Rejections under 35 USC 112, second paragraph. Since no terminal disclaimer or arguments traversing the Examiner's position have been provided, this rejection is maintained for the reasons of record.

Conclusion

17. No claim is in condition for allowance.

18. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez, Ph.D., whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert B. Mondesi, can be reached at (571) 272-0956. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Primary Patent Examiner
Art Unit 1652

DR
August 9, 2011